PH and Connective Tissue Disease

Guest editor Stephen Mathai, MD, MHS led a group of distinguished clinician researchers in an invigorating discussion of controversial issues related to the evaluation and management of PH patients with scleroderma. Contributing to the conversation were Virginia Steen, MD, Professor of Medicine, Georgetown University; Laura Hummers, MD, Associate Professor of Medicine, Johns Hopkins Medical Center, and Rajan Saggar, MD, Associate Professor of Medicine University of California, Los Angeles.

Dr Mathai: I'd like to thank the panelists for joining our roundtable today. I'm thrilled to have such a distinguished group of experts in the field of scleroderma and pulmonary hypertension join us. We have Virginia Steen from Georgetown University, who is professor of medicine and a rheumatologist; we have Laura Hummers, who is an associate professor of medicine at Johns Hopkins, also a rheumatologist; Rajan Saggar, associate professor of medicine from UCLA, who is a pulmonologist. I'd like to thank you all for participating today. What I'd like to do is take some time to discuss some of the more controversial issues in the evaluation and management of patients with scleroderma and pulmonary hypertension, and really focus on the unique features of scleroderma as it pertains to pulmonary hypertension, then also as it relates to management of extra-pulmonary disease that can impact pulmonary hypertension. So with that, I'd like to start our discussion by talking about our approach to screening. With the advent of the DETECT study, which describes an algorithm that can be employed to largely successfully identify patients with pulmonary hypertension, I'd like to get an idea from the panel how they view the results of this study and whether this is the approach that they have adopted in their clinical practice. So Gini, would you like to start?

Dr Steen: Sure. I have had a little bit of difficulty with the DETECT study; I think primarily because the features on the echocardiogram are not always the ones that the routine echocardiograms give. And then to have—particularly rheumatologists—go through all these other things to get this algorithm that, if you're in the United States, you can't even use. So it's not been a very practical tool, I don't think, for the rheumatology community as a whole. And it doesn't allow them to think about it, which I think is really important. So when you look at the data from DETECT, there have been numerous studies that show it has high sensitivity and specificity. But also if you look at the European Respiratory Society and the other European society that had their evaluation, which was just done on echo, and then the Australian scleroderma interest group that really was based on the FVC (forced vital capacity) to DLCO (pulmonary diffusing capacity) ratio and the NT pro-BNP (N-terminal pro-brain natriuretic peptide), all of those "formulas" or algorithms all have sort of very, very similar specificity and sensitivity and yet actually DETECT has the highest false negative rate, as far as doing more caths that are normal. So yes, it is good. It's important to think about all those things. I'm just not quite sure how practical it is for the practicing rheumatologist. Laura, what do you think?

Dr Hummers: I think I agree. I certainly agree with the practical aspects that you pointed out in terms of getting the appropriate measures on echocardiogram. I think there's such wide heterogeneity in how echocardiograms are reported back to us, that I find that that doesn't really help us that much. And there are aspects I think that we're just not used to in the algorithm and don't often have, at least, so I don't have a good clinical sense of how to use them, such as uric acid.

Dr Steen: I was going to say, you don't get a uric acid on all your scleroderma patients (laughter)?

Dr Hummers: (laughter) I have not. And it's actually not part of our comprehensive metabolic panel in our system. So we don't get it, even in our routine lab work, so it's something you have to think about. So I think while I agree with you that the data are compelling, we also have to keep in mind that this is not an all-comers scleroderma cohort that DETECT utilized. It was a high-risk cohort. So I think taking that and using that for all of our scleroderma patients in terms of a routine screening algorithm, I think we don't really have the data to support that, based on DETECT. I think when we think about screening all of our patients we can all agree that probably the best initial screening approach is based on pulmonary function tests. And again, the DETECT algorithm, all the patients had a low DLCO, so this was again a high-risk population for having pulmonary vascular disease. I think the field is moving towards the concept of a two-step screening process perhaps, that maybe we don't always need to get the echocardiogram as a matter of course for every patient every year, as has been the practice, especially in a patient who is asymptomatic, with a very normal DLCO. I agree with the way the field is moving in that way, but that's not necessarily based on data from DETECT.

Dr Mathai: So Rajan, I was wondering if you could comment from a pulmonologist's point of view regarding your impression of DETECT and to maybe describe what you do in your practice, if it differs from the DETECT algorithm?

Dr Saggar: I appreciate the points made by both of you. But I actually think that this is an algorithm that, much

like the European guidelines that Dr. Steen brought up, uses a lot of the same criteria in terms of the parameters that we're looking at. The reason I actually like it is because I look at it a little bit differently, in the sense that if you take all sclerodermas—and we all are worried about pulmonary vascular disease in our scleroderma patients—I find that I get quite a number of referrals for estimated pulmonary pressures that are just above the upper limits of normal from whichever echocardiography lab the patient may be coming from. So, I like the idea of enriching the initial evaluation, if you will. For instance, DETECT used cutoffs for DLCO <60% and FVC >40% to enrich the population for pulmonary vascular disease. Plus, some of the work which has been done by Dr. Steen with FVC/DLCO ratio and other parameters such as NT pro-BNP and right axis deviation on the EKG are all helpful. There is a nice report recently by the Kovacs group just looking at WHO Group 1 PAH and they evaluated three very simple parameters including NT pro-BNP, resting oxygenation (>95.2% at rest on room air), and electrocardiographic right axis deviation. Essentially, what the authors were saying was that if you did not have right axis deviation and you had a normal NT pro-BNP and a normal resting oximetry at rest on room air, your chances of having PAH were next to zero. While that may seem obvious—or sometimes may seem obvious—I think right axis deviation is something that a lot of people may not necessarily think of right away in terms of getting a 12-lead EKG on your first visit to evaluate for this parameter. So I think there are several important screening parameters which all have merit. I think how we best use these parameters so we don't miss PAH cases and so we don't do extra right heart catheterizations is always, is tough to hone in perfectly on, but really the key issue.

Dr Mathai: That's an interesting perspective. I think the comments made here are very relevant. What I wonder is what is the end game of the screening? We know that we are talking about an at-risk population for which the prevalence of PAH is relatively high, which is unique. We don't have any other at-risk cohort in which that risk is as high or as well defined where we know that the prevalence of PAH or the incidence of PAH will be significant enough to warrant screening. So I think that is an important factor. And while what you're describing, Rajan, regarding right axis deviation is clearly important and obviously indicates progressive pulmonary vascular disease, are we potentially missing early identification if we focus on that? I realize you're not saying that we focus solely on that; but I'm wondering if what we're talking about, in the context of scleroderma, is that we should be looking for more subtle signs and perhaps identifying earlier disease in hopes of intervening earlier.

Dr Steen: I think there's pretty good data that there's better survival and better outcome if you identify them early. Now, whether that changes the whole course of the disease or you're just uncovering early disease that's not going to get bad, that we don't know. But certainly, if you wait until somebody comes to a pulmonologist with functional class III as opposed to being started on treatment at a functional class II, survival is better, outcomes are better. I think both in PHAROS and our studies, as well as the French and Australian both have studies that have shown that. Now, whether that's, as I say, changing the whole pathophysiology or just really treating milder disease that maybe we didn't know before—we've certainly seen enough patients that go downhill so rapidly without treatment—that I'm not sure there's a large "mild PH" that doesn't get worse. I'm not sure.

Dr Saggar: I would just add to that that with all the heterogeneity that this disease has in terms of how it can present with pulmonary hypertension—which I find to be the most difficult part of dealing with pulmonary hypertension and scleroderma—trying to tease out which type of PH your patient actually has (Group 1, 2, or 3) while keeping in mind that the prognosis of each PH type is different and probably also different depending on what point in the disease course you pick the disease i.e. earlier in the game or later in the game, is to me a very difficult thing. I'm trying to think to myself, in my own practice, how many times I've actually seen patients who did not have pulmonary hypertension Group 1—let's just leave it at Group 1 right now (PAH)—and I was clinically following them and I watched literally under my own nose, as they developed PAH. The cases I can remember of that happening are quite few. In other words, most patients who come to me arrive with the PH diagnosis or with a concern for the diagnosis. But if I consider the patients that come to me and do not have PH and subsequently develop it under my own care; it's been very few. But when it has happened, it's been abrupt. Interestingly, these patients don't appear to start off with mild disease and slowly progress. PH was either not there or suddenly it's severe and present. I really haven't seen the middle ground group and as such, I haven't seen them evolve the way I think we'd like to see the disease sort of evolve and then perhaps have the opportunity to change the natural history of the disease. I don't know; I would be interested to hear what everyone else thinks about that.

Dr Steen: I think you're absolutely right, that for most patients, it doesn't sneak up on them. I mean, we follow—Laura and I—follow people that have had low DLCOs for years and years and years and they don't ever get it. And yet somebody that's had a low DLCO for years and years can present with pulmonary hypertension just acutely.

Dr Mathai: That's a great segue, because I want to ask that question to Laura. So what, if we're thinking about screening algorithms, whether DETECT or another algorithm you employ, what do you do with a patient who has a positive screen one year, undergoes the definitive study, the right heart catheterization, and ends up not having pulmonary hypertension? What do you do in the subsequent year? Because that person is likely to screen positive again. So how do you approach those types of patients?

Dr Hummers: Well, I think a lot of it is about what the clinical presentation

is and what the deltas are. So we are often screening based on somebody with symptoms usually, at least mild symptoms, and the most typical scenario is somebody with a falling DLCO. And whether or not their echo is abnormal, we might, if they're dyspneic and we don't have another clear explanation, we might refer that group for cath. So I think that would probably be the most common scenario that you would be talking about where we have a suspicion, they're obviously in that risk population, and we cath them and it's typically not totally normal, right? It's below 25 though; their mean PA pressure is below 25. So to me, it really depends on symptom progression or change in their screening tests. That would usually be either DLCO changing or pro-BNP levels changing and/or dyspnea changing that would make me consider retesting them.

Dr Steen: The other area is the 6-minute walk with new hypoxia, which is what we found in PHAROS, which was another parameter clearly associated with the new development of pulmonary arterial hypertension. And that's easy to do when you're doing your yearly tests and I think that's something that we should do. Again, with the understanding that they should be using forehead probes and not finger probes. (laughter) Which is a challenge in many community pulmonary labs that don't see a lot of scleroderma.

Dr Mathai: Gini, were there any other parameters on the 6-minute walk test that were useful as a screening tool?

Dr Steen: We did not look at anything, other than the—I mean, we looked at obviously distance and the Borg dyspnea score and the oxygen desaturation was a 4% decrease from resting, so that's what we ended up using. Greater than 4%.

Dr Saggar: Yeah. Can I just make a comment about, just from my own thoughts about DLCO in this population? Correct me if I'm wrong. I would love to hear from the panel regarding DLCO. When you look at, let's say some of the REVEAL literature focusing on the connective tissue disease cohort of the PAH group, the systemic sclerosis group that has PAH, when you compare it to idiopathic PAH, they have lower diffusing capacities, statistically lower. So it seems like it's almost like how low is too low in the delta? And we're all worried about it, and I get that. I guess the question I'm struck by is: when you're looking at that, how many people would I see whose delta concerns me? I'm often surprised that they don't have pulmonary hypertension when I look for it. And then, the other thing that I found was striking was, Ron Oudiz actually had a grant to study patients who had an objective abnormal exercise response without resting pulmonary hypertension. He followed a large cohort of these patients at Harbor-UCLA and, although he hasn't published this yet, he hasn't seen a single patient develop pulmonary hypertension who had an abnormal exercise response at baseline. Perhaps that may not be the right variable; we can always argue that. But, that is an objective variable and we didn't see a single case. So I think there may be factors that we just don't really understand even with the deltas that we are all so concerned about. It doesn't always hit, I guess is what I'm saying.

Dr Steen: No. I did try for years to use the exercise echo and the exercise cath to predict and it does predict, but it doesn't predict pulmonary arterial hypertension. They certainly—40% of those patients that did develop later pulmonary hypertension had pulmonary venous hypertension—so it wasn't quite as good as I had hoped and anticipated, but…..

Dr Saggar: Yeah, what do you think, Laura?

Dr Hummers: In terms of using exercise studies?

Dr Saggar: No, just the DLCO.

Dr Hummers: DLCO tends to be obviously the most variable of the parameters that we're looking at on PFT. So using that alone can be problematic. We follow patients over pretty long periods of time and these are things that are typically not evolving over short periods of time, so we tend to have multiple data points, and so I'll just end up screening more often if I see somebody have a change in their DLCO to confirm. And again, to me, if the patient presents with a change in symptoms to go along with that, I'm obviously more likely to be worried about that delta DLCO in that scenario.

Dr Saggar: Yeah, and I think that's exactly the point, right? You're looking; we're all kind of looking. One parameter alone, of course, does not seem to cut it. I mean, it scares us when a DL drops by 20%; first thing you want to do is actually repeat it, especially if the patient tells you, "Look, I feel fine." But I think your point is well taken, and that's where the subjectivity comes in. In some of these patients, it all boils down to what they're comparing their current symptoms to. If they had a prior event in an ICU where they were very short of breath and, they had some really bad pneumonias, they're feeling pretty good and to them, where they are now is good enough. So they don't really report the symptoms. So a lot of that becomes, what kind of symptoms can you get out of the patient ? How bad is their quality of life and what's driving those complaints? Obviously, there are many different reasons to be short of breath on exertion. I think that's what makes it so difficult, teasing out when you have the real deal or when you're dealing with something else.

Dr Hummers: I agree. And we're picking up some patients now who have screening signs of possible development of pulmonary hypertension. They're older when they develop scleroderma. They've had scleroderma for a long period of time. They have a very low DLCO, in the 40% to 50% range. So your suspicion is high, but they're completely asymptomatic, at least with the level of activity that they're doing. They may not be all the most active people but they're asymptomatic completely. I've had conversations with some of these patients when I've said, "We can do this test and determine if you have pulmonary hypertension, certainly

more definitively." But they may not be interested in taking another medication and I've followed them because it's not clear that we're going to make anything better, right? Because if they're asymptomatic at baseline, it's not clear that they're going to make anything better by doing that. I've followed some patients like that, with this—like Gini said, with these DLCOs that are low but they clinically remain stable over long periods of time. They're not particularly symptomatic.

Dr Saggar: Yes, exactly.

Dr Steen: So another area, which changes the topic just a little bit, is the group of patients that have ILD, who have sort of a ratio of the FVC to DLCO that's, 1.3 or 1.4, who then develop worsening DLCO and get a higher ratio. I don't have enough numbers, but I think those are the ones that are getting pulmonary hypertension, whether it's secondary to their ILD or whether it's the group that we all struggle with that has some ILD but then develops pulmonary vascular on top of it. And that group I think is the one that we all struggle probably even more than the pulmonary arterial, pure pulmonary arterial hypertension group, because no two people manage that group of patients the same. And nobody really knows what to do with them.

Dr Mathai: Well, Gini, that's a wonderful segue into what I want to go to next, which is talking about approach to treatment. I think that we can start with talking about how we approach patients who fit that particular phenotype; patients who have interstitial lung disease and pulmonary hypertension. I know that Rajan's experience at UCLA with using pulmonary vasodilator therapy has been somewhat successful and perhaps a little bit of a different experience from what Laura and I have experienced at Hopkins. And I'd be curious, Gini, about your take on that, as well. So Rajan, if you want to give us your experience with this and how you approach patients. Are there thresholds that you use, either for degree of pulmonary vascular disease, degree of pulmonary hypertension, degree of interstitial lung disease, that dictate how you approach the management?

Dr Saggar: Well, as you know, Steve, this is a very difficult and controversial topic. When I first started doing this, my approach was a very simple one. I had patients in front of me who had clear pulmonary fibrosis; there was no question radiographically or by pulmonary function testing who had developed, either before or after the pulmonary fibrosis, pulmonary vascular disease. And let's call it severe, not subtle. And the question in front of me was, well, we really have three options. One was to say: "Well, this is a patient who needs a lung transplant," which I think all of us would agree when you have significant severity of both conditions. Obviously those patients tend to do the worst in terms of survival, etc., and morbidity, so transplantation makes a lot of sense. But as we all know, transplantation is not an option for everyone, for various reasons. And one of the biggest reasons early on was that a lot of the centers were simply not transplanting patients with scleroderma, for a whole host of other reasons, which we may get into. So lung transplantation may have been an option for a small percentage of patients, but that left a group that we really were just kind of "Well, what now?" And so now, a lot of these patients were already on some type of immunomodulation for their pulmonary fibrosis. Their pulmonary fibrosis in these settings may or may not be stable, but I tend to find that radiographically, it is stable, in the setting of developing this severe pulmonary hypertension phenotype. And if there is a change, it might be just related in fact to the mild restriction that we see in patients who have PAH. But then the question became, "Should we treat these patients?" And, as you know, the alternative was essentially an early demise. So our concept was, I think, a reasonable, coordinated approach where we had some thoughts on who the best patients were to first treat. So the first patients we chose to treat were patients who had clear evidence for right heart dysfunction or frank right heart failure. And one of our discussion points was always, well, look, there's no question this patient has right heart failure. There's clear volume overload. The exam is consistent with right-sided congestive heart failure. And we know that this patient's pulmonary vascular disease must be severe. And then we'd prove it, based on echocardiography and right heart catheterization. We chose to treat those patients as if they had sort of form of Group 1 PAH, on top of, if you will, a pulmonary fibrosis background. It's a little bit difficult because the whole definition of Group 1 versus Group 3 is based on how much lung disease you have. But I think my opinion over the years has become that there truly are patients who have autoimmune disease, systemic sclerosis and others, that truly have two conditions. One is their parenchymal lung disease and one is their pulmonary vascular disease. I, for one, believe that those patients can be treated with vasodilator therapies successfully. Again, it's anecdotal. We do not have randomized, placebo-controlled data. And currently, everyone would agree that there is no best practice for this. I think that goes without saying. But I do believe that we have an opportunity here to help some of these patients. And teasing out that subgroup is, I think, really the name of the game here.

Dr Mathai: Laura or Gini, thoughts on what Rajan has said? And perhaps giving us your opinion and approach to these types of patients?

Dr Hummers: Well, I think I would agree with everything that was just said. I think I agree that there are groups of patients who have interstitial lung disease who can have very stable interstitial lung disease of various degrees of severity, but appear as best we can tell, completely stable from an ILD standpoint, either on therapy or off therapy, depending on the severity of their disease and whether it was treated, who then seem to develop significant pulmonary vascular disease. I would argue that it's not purely just based on their interstitial lung disease, both in terms of degrees of severity of their ILD, but also the stability. If you look at the timing at which they develop it, it seems to at

least be compatible with when other patients with scleroderma are developing pulmonary vascular disease. So I do think that a large subgroup of these patients probably do have two processes going on that may not totally be independent of each other, but suggest that there is a primary pulmonary vascular process that evolves. I think Steve and I have experience that has been variable in terms of management of those patients where we've addressed their ILD, if that's present, if they require therapy for that. And when we use vasodilator therapy, I think we've had high degree of variability in terms of how somebody responds to vasodilators in that population. I think we're really not very good at predicting what that response could be, based on any of the parameters that we look at, either the severity of their pulmonary hypertension, and, obviously, we look at the severity of their ILD. We've had some patients with very severe ILD tolerate vasodilators fairly well and patients who seem to not have as severe ILD not tolerate vasodilators very well, due to seemingly worsening of their hypoxia. So I think all patients in that scenario probably should deserve a consideration for trials of vasodilators. But again, I think we don't have enough data to guide us and, on a practical level, haven't been able to identify those patients who may respond or who may do poorly on pulmonary vasodilators.

Dr Mathai: Thank you. Gini, are there any specific therapies that you might think of earlier for patients with interstitial lung disease-associated pulmonary hypertension? Or is it any drug, any pulmonary vasodilator?

Dr Steen: Well, I happen to work with a pulmonologist right now who is really afraid of using (laughter) a PDE5 in these patients. So we have ended up going to the inhaled prostacyclins first. And I personally think, in my experience again, that our patients do tolerate the PDE5s, even though they have significant interstitial disease. Most of these are not people that have severe hypoxia already. And it doesn't seem to be worsening. I haven't had much excitement about the ERAs in this setting at all. And certainly, with some of the other studies (laughter), it's been a little bit anxious (laughter) using them. But, I think that Raj's paper was showing that the IV drugs actually can work very well in some of these patients. I agree that we should at least give them a try. I've had patients that, three years later, have been able to actually even taper their—not taper off, but taper the higher doses of them and are still doing all right. So, I don't think we can be quite as dogmatic. I mean, there's some people that are just have bad ILD; we're not going to do anything for them. I just don't think you can be that way.

Dr Mathai: So this leads to the next area I want to talk about: how do you assess response, not only in your ILD/PH patients but in your scleroderma-PAH patients? We know the limitations of perhaps the commonly used outcome measures in clinical trials and how they might be not as representative or reflective of response to therapy in our scleroderma population, namely the 6-minute walk test, for instance, or time to clinical worsening, which may be confounded by other potential reasons for a patient to be hospitalized. But I'm curious about how each of you approaches assessing response and is there some formula that you follow with specific testing that you do to assess response?

Dr Steen: Well, let Raj start with that.

Dr Saggar: Well, that's also a tough question. I think I can say that, in general I find that when we treat patients who have scleroderma and PAH—I think standardly in PAH—people get better. They seem to get better. And they really go from feeling pretty awful to getting some relief. And they're pretty happy with that because they come to clinic saying, "Hey, I definitely feel better." And I think we sort of lost some ground over the years, just kind of with that, "Hey, how do you feel? You feel well? Okay. Well, then I think we'll stay where we are." But as you guys have done at Hopkins and obviously the AMBITION combination approach, there seems to be mounting data that this is the way to go. I think we're even seeing more improvements. So with that in mind, with my patients, I sort of pick a couple, three activities that they do, that they often have to stop multiple times while they're doing it and I document what those activities are and how many times they stop and their baseline, much like we do with the baseline 6-minute walk. I track those common daily activities that they tend to do. That's been helpful for me from a subjective standpoint, in terms of improving my ability to understand where they are when they come to clinic and how far they are from both their baseline and normal. I also try to determine what they could do normally a few years prior, essentially. Objectively though, aside from the 6-minute walk, I think the echocardiographic assessments when you're working together, side-by-side with cardiologists who are interested in pulmonary vascular disease and you have a well orchestrated echocardiographic protocol where you're really focused on the right ventricular function in all the different objective aspects that we're able to assess today, it's been very helpful for me to include those criteria, as well. So I'm pretty aggressive about getting frequent echocardiograms. I think I reserve right heart catheterizations really for when I'm going to add additional therapy or if I'm just confused about what their real response was to the original medical therapy. Every once in a while I use a cardiopulmonary exercise test for various reasons, but that's really into my mixed sort of patients who have multiple issues that can contribute to pulmonary hypertension or to their dyspnea. That's been helpful, but that's not a common event in my practice.

Dr Mathai: Any other things that you do, Laura or Gini, when you're following these patients or things you look for?

Dr Steen: At this point, with all the medications that are now available and particularly beyond PD5s and ERAs, I think I'm really more and more dependent on my PH person than I ever have been (laughter). It's just these patients get very, very complicated for a rheumatologist. I mean, I focus on

the rheumatology aspect of it and try to help monitor, make sure that there aren't other things going on. I think I've tended to follow the NT pro-BNP more so than any other, but maybe that's just because it's an easy number (laughter) for me to look at. As I said, I think that there's so much going on that it really requires a PH person these days.

Dr Hummers: I would agree with that. I feel like most of the determinations are being made in terms of escalation of therapy at least and response to therapy, both based with our pulmonology colleagues, with Steve and the group. I do think there is a subset of patients for which, at the group level, 6-minute walk is problematic, but I think there's a reasonable subset of patients with scleroderma where 6-minute walk is still a pretty reasonable surrogate for response. So I think in that subgroup, continuing to do the 6-minute walk makes sense. And I think again, it's a good surrogate for functionally how the patient is doing. I don't find that often we get routine echoes; maybe we're not as systematic here in terms of getting the echoes. But we've certainly had patients where changes in some of the right-sided parameters by echo were the main reason, even in a somewhat stable patient on therapy, to consider change of therapy. I feel like that doesn't happen as often as changes in functional class or decline in 6-minute walk in a patient where you think the 6-minute walk is a reasonable test.

Dr Saggar: So Steve, I was just going to add that I forgot about the serologic evaluation. So NT pro-BNP, BNP, and I have to say add the cardiac MRI, as well. You folks have done some outstanding work at Hopkins and others have, as well. We just have a really tough time getting the MRIs as routinely as we'd like. I think if it was readily available for us, in terms of our insurers and other obstacles, we would be much more aggressive about using them. I think the data, as you guys have shown nicely and others have, as well, really seem to be even a more objective way of looking at the entire cardiopulmonary system in real time. So, I'm sure you would have a lot to say about that.

Dr Mathai: (laughter) Yes, well I think there are many ways of examining these patients. I think we still have a lot of work to do to better understand which of these particular metrics is the most useful. It may end up that it's more than one; it would be a combination of how a patient is feeling and maybe we need to be more dogmatic about assessing that uniformly, really understanding how a patient feels with some sort of validated questionnaire and then just following that over time as an additional piece of information that might help us determine response.

I want to add one last topic. I can't let our rheumatologists off the hook without commenting on the role of immunosuppression in the management of these patients. I know that obviously there are specific indications for immunosuppression in scleroderma patients, whether it be myositis, progressive skin disease, or progressive lung disease, but I'm intrigued by current studies that are going on with immunosuppressive or immunomodulatory agents in the treatment of pulmonary arterial hypertension in the setting of scleroderma. I'm curious about your thoughts regarding the potential role for those types of therapies for the management of this patient population.

Dr Hummers: Gini, go ahead. (laughter)

Dr Steen: Thanks, Laura. I think the answer is still unknown (laughter), Steve. You know some of our PHAROS observational studies suggested that maybe CellCept® might do something, but it's so observational, mostly in people that had a little bit of restrictive disease. The data on rituximab is still out. You know, I'm much more of a believer of the inflammation or immunologic pathogenic effects on PH. We just had the International Scleroderma Workshop and Mark Nicolls gave a beautiful lecture on that. And, as I said, I'm certainly much more of a believer than I was ten years ago, when I first met Mark and he tried to convince me. I think that that might be a role in the future. I mean, and if our data on CellCept® is real. There is also the bardoxolone clinical trial; all that is beginning to play a role. We'll see whether it's real or not. But I still think that the answer is not clear.

Dr Hummers: I would agree. I think we don't have enough good data yet to really support the use of any immunosuppressant. I think it might be something going forward; the data certainly is intriguing. I certainly agree with the studies that are going on; but I think not ready for primetime yet. But I think we should keep looking.

Dr Mathai: So speaking of novel therapies, I know that Gini brought up bardoxolone and there are other studies that are specifically targeting patients with scleroderma and pulmonary hypertension. One smaller study is of ifetroban, a thromboxane A2/prostaglandin H2 receptor inhibitor. I'm curious, Laura, if you have any particular thoughts about these novel mechanisms and just general thoughts about focusing on patients with scleroderma and pulmonary hypertension and how that might be important going forward.

Dr Hummers: Well, I think we all will agree that scleroderma/pulmonary hypertension is certainly unique among all the various etiologies of pulmonary hypertension. There are these multiple competing issues that could be driving the disease, right? So there are the effects of interstitial lung disease. There's the primary myocardial disease that might be playing a role. There's the pulmonary vascular disease. So I think the approach to identify targets beyond the usual targets that would be considered in pulmonary arterial hypertension makes sense, because this is clearly not just one process. So I agree with the approach. Whether the targets are correct, I think obviously time will tell and data will tell. But I think the approach is correct.

Dr Mathai: I think that's a perfect place to end. I'd like to thank the members of the roundtable, Dr Gini Steen, Dr Rajan Saggar, and Dr Laura Hummers, for participating. And thank you again.